CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074654

Trade Name : ORPHENADRINE CITRATE, ASPIRIN AND CAFFEINE TABLETS

Generic Name: Orphenadrine Citrate, Aspirin and Caffine Tablets

Sponsor : Eon Labs Manufacturing, Inc.

Approval Date: December 31, 1996

ANDA 74-654

DEC 31 1996

Eon Labs Manufacturing, Inc.
Attention: Amal Shaker
227-15 N. Conduit Avenue
Laurelton, NY 11413

Dear Sir:

This is in reference to your abbreviated new drug application dated March 24, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg.

Reference is also made to your amendment dated October 24, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg are bioequivalent, and, therefore, therapeutically equivalent, to those of the listed drugs (Norgesic™ and Norgesic™ Forte Tablets, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg, respectively, of 3M Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

D. L. Sporn 12/31/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Orphenadrine Citrate, Aspirin, And Caffeine Tablets
Final Printed Labels

NDC 0185-0713-01

DEC 3 1 1996

Exp. Date:

Lot No.:

USUAL DOSAGE: Adults: 1 to 2 tablets 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

25 mg/385 mg/30 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate ... 25 mg
Aspirin ..... 385 mg
Caffeine ..... 30 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0713-01 1

NDC 0185-0713-05

DEC 3 1 19

Exp. Date:

Lot No.:

USUAL DOSAGE : Adults: 1 to 2 tablets 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

25 mg/385 mg/30 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate .... 25 mg
Aspirin ..... 385 mg
Caffeine ..... 30 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0713-05 9

NDC 0185-0713-10

DEC 3 1

Exp. Date:

Lot No.:

USUAL DOSAGE : Adults: 1 to 2 tablets 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

25 mg/385 mg/30 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate .... 25 mg
Aspirin ..... 385 mg
Caffeine ..... 30 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0713-10 3

Orphenadrine Citrate, Aspirin, And Caffeine Tablets
Final Printed Labels

NDC 0185-0714-01

Lot No.:
Exp. Date:

USUAL DOSAGE: Adults: One half to 1 tablet 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

50 mg/770 mg/60 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate ... 50 mg
Aspirin ..... 770 mg
Caffeine ..... 60 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0714-01 8

NDC 0185-0714-05

Lot No.:
Exp. Date:

USUAL DOSAGE: Adults: One half to 1 tablet 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

50 mg/770 mg/60 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate ... 50 mg
Aspirin ..... 770 mg
Caffeine ..... 60 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0714-05 6

NDC 0185-0714-10

Lot No.:
Exp. Date:

USUAL DOSAGE: Adults: One half to 1 tablet 3 to 4 times daily. See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/96

Orphenadrine Citrate, Aspirin, And Caffeine Tablets

50 mg/770 mg/60 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Eon Labs

Each tablet contains:
Orphenadrine Citrate .... 50 mg
Aspirin ..... 770 mg
Caffeine ..... 60 mg

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

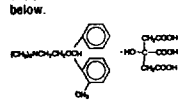
N 3 0185-0714-10 0

ORPHENADRINE CITRATE, ASPIRIN, AND CAFFEINE TABLETS

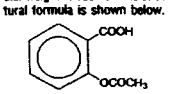
DESCRIPTION:

Each tablet, for oral administration, contains Orphenadrine Citrate USP, 25 mg or 50 mg, Aspirin USP, 385 mg or 770 mg, Caffeine USP, 30 mg or 60 mg.

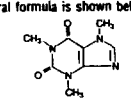
Orphenadrine citrate, *N*, *N*-Dimethyl-2-[(o-methyl-α- phenylbenzyl)oxy]ethylamine citrate (1:1), is a centrally acting (brain stem) compound. It occurs as a white, practically odorless, crystalline powder, having a bitter taste. Its molecular formula is $C_{18}H_{23}NO.C_6H_8O_7$ with a molecular weight of 461.51. The structural formula is shown below.



Aspirin, salicylic acid acetate, is a non-opiate analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle like powder and is odorless or has a faint odor. Its molecular formula is $C_9H_8O_4$, with a molecular weight of 180.16. The structural formula is shown below.



Caffeine, 1,3,7-trimethylxanthine, is a central nervous system stimulant which occurs as a white powder or white glistening needles. It also has a bitter taste. Its molecular formula is $C_8H_{10}N_4O_2$, with a molecular weight of 194.19. The structural formula is shown below.



Each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, FD&C Blue No. 1, FD&C Yellow No. 10, anhydrous lactose, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and sodium lauryl sulfate.

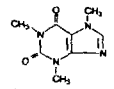
CLINICAL PHARMACOLOGY:

Orphenadrine citrate is a centrally acting (brain stem) compound which in animals selectively blocks facilitatory functions of the reticular formation. Orphenadrine does not produce myoneural block, nor does it affect crossed extensor reflexes. Orphenadrine prevents nicotine-induced convulsions but not those produced by strychnine.

Chronic administration of Orphenadrine Citrate, Aspirin, and Caffeine to dogs and rats has revealed no drug-related toxicity. No blood or urine changes were observed, nor were there any macroscopic or microscopic pathological changes detected. Extensive experience with combinations containing aspirin and caffeine has established them as safe agents. The addition of orphenadrine citrate does not alter the toxicity of aspirin and caffeine.

The mode of therapeutic action of orphenadrine has not been clearly identified, but may be related to its analgesic proper-

tural formula is shown below.



Each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, FD&C Blue No. 1, FD&C Yellow No. 10, anhydrous lactose, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY:
Orphenadrine citrate is a centrally acting (brain stem) compound which in animals selectively blocks facilitatory functions of the reticular formation. Orphenadrine does not produce myoneural block, nor does it affect crossed extensor reflexes. Orphenadrine prevents nicotine-induced convulsions but not those produced by strychnine.

Chronic administration of Orphenadrine Citrate, Aspirin, and Caffeine to dogs and rats has revealed no drug-related toxicity. No blood or urine changes were observed, nor were there any macroscopic or microscopic pathological changes detected. Extensive experience with combinations containing aspirin and caffeine has established them as safe agents. The addition of orpheradrine citrate does not alter the toxicity of aspirin and caffeine.

The mode of therapeutic action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anticholinergic actions.

INDICATIONS AND USAGE:
1. Symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.
2. The orphenadrine component is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions.

   The mode of action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Orphenadrine Citrate, Aspirin, and Caffeine Tablets do not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS:
Because of the mild anticholinergic effect of orphenadrine, Orphenadrine Citrate, Aspirin, and Caffeine Tablets should not be used in patients with glaucoma, pyloric or duodenal obstruction, achalasia, prostatic hypertrophy or obstructions at the bladder neck. Orphenadrine Citrate, Aspirin, and Caffeine Tablets are also contraindicated in patients with myasthenia gravis and in patients known to be sensitive to aspirin or caffeine.

The drug is contraindicated in patients who have demonstrated a previous hypersensitivity to the drug.

WARNINGS:
Reye's Syndrome may develop in individuals who have chicken pox, influenza, or flu symptoms. Some studies suggest possible association between the development of Reye's Syndrome and the use of

medicines containing salicylate or aspirin. Orphenadrine Citrate, Aspirin, and Caffeine Tablets contain aspirin and therefore are not recommended for use in patients with chicken pox, influenza, or flu symptoms.

Orphenadrine Citrate, Aspirin, and Caffeine Tablets may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

Aspirin should be used with extreme caution in the presence of peptic ulcers and coagulation abnormalities.

USAGE IN PREGNANCY:
Since safety of the use of this preparation in pregnancy, during lactation, or in the childbearing age has not been established, use of the drug in such patients requires that the potential benefits of the drug be weighed against its possible hazard to the mother and child.

USAGE IN CHILDREN:
The safe and effective use of this drug in children has not been established. Usage of this drug in children under 12 years of age is not recommended.

PRECAUTIONS:
Confusion, anxiety and tremors have been reported in a few patients receiving propoxyphene and orphenadrine concomitantly. As these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of one or both agents is recommended in such cases.

Safety of continuous long term therapy with Orphenadrine Citrate, Aspirin, and Caffeine Tablets has not been established; therefore, if Orphenadrine Citrate, Aspirin, and Caffeine Tablets are prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS:
Side effects of Orphenadrine Citrate, Aspirin, and Caffeine Tablets are those seen with aspirin and caffeine or those usually associated with mild anticholinergic agents. These may include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, dilation of the pupil, increased intraocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, and rarely, urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of confusion. Mild central excitation and occasional hallucinations may be observed. These mild side effects can usually be eliminated by reduction in dosage. One case of aplastic anemia associated with the use of Orphenadrine Citrate, Aspirin, and Caffeine Tablets has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Orphenadrine Citrate, Aspirin, and Caffeine Tablets. Some patients may experience transient episodes of lightheadedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION:
Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg: Adults 1 to 2 tablets 3 to 4 times daily.

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 50 mg/770 mg/60 mg: Adults 1/2 to 1 tablet 3 to 4 times daily.

HOW SUPPLIED:
Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg are supplied as round, layered tablets colored white and green, imprinted E713 and are available in bottles of 100, 500, and 1000.

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 50 mg/770 mg/60 mg are supplied as scored, capsule-shaped, layered tablets colored white and green, imprinted E714 and are available in bottles of 100 and 1000.

STORAGE:
Store at controlled room temperature 15°- 30°C (59°-86°F).

Protect from moisture.

CAUTION:
Federal law prohibits dispensing without prescription.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

may include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, dilation of the pupil, increased intraocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, and rarely, urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of confusion. Mild central excitation and occasional hallucinations may be observed. These mild side effects can usually be eliminated by reduction in dosage. One case of aplastic anemia associated with the use of Orphenadrine Citrate, Aspirin, and Caffeine Tablets has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Orphenadrine Citrate, Aspirin, and Caffeine Tablets. Some patients may experience transient episodes of lightheadedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION:

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg: Adults 1 to 2 tablets 3 to 4 times daily.

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 50 mg/770 mg/60 mg: Adults 1/2 to 1 tablet 3 to 4 times daily.

HOW SUPPLIED:

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 25 mg/385 mg/30 mg are supplied as round, layered tablets colored white and green, imprinted ℰ713 and are available in bottles of 100, 500, and 1000.

Orphenadrine Citrate, Aspirin, and Caffeine Tablets, 50 mg/770 mg/60 mg are supplied as scored, capsule-shaped, layered tablets colored white and green, imprinted ℰ714 and are available in bottles of 100 and 1000.

STORAGE:

Store at controlled room temperature 15°- 30°C (59°-86°F).

Protect from moisture.

CAUTION:

Federal law prohibits dispensing without prescription.

Manufactured by:
Edn Labs Manufacturing, Inc.
Laurelton, NY 11413

Issued 7/96
MF0713REV0796
Flat# 11818

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. **CHEMIST'S REVIEW NO.:** No.4

2. **ANDA #:** 74-654

3. **NAME AND ADDRESS OF APPLICANT:**
Eon Labs Manufacturing, Inc.
Attention: Amal Shaker
227-15 N. Conduit Avenue, Laurelton, NY 11413

4. **LEGAL BASIS FOR ANDA SUBMISSION:** See CR #1

5. **SUPPLEMENTS(s):** N/A 6. **PROPRIETARY NAME:** None used

7. **NONPROPRIETARY NAME:**
Orphenadrine Citrate, Aspirin, and Caffeine Tablets

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Eon

03/24/95	ANDA submission (received at OGD on 03/28/95)
06/02/95	Amendment (Re:refuse-to-file letter of 04/24/95)
07/21/95	Amendment (Re:refuse-to-file letter of 07/06/95)
04/19/96	Amendment (MAJOR) (response to NA letter of 01/29/96)
04/22/96	Amendment (response to bio deficiency letter of 01/18/96)
08/22/96	Amendment (response to NA letter of 07/24/96)
10/24/96*	Amendment (response to NA letter of 09/24/96)

FDA

04/24/95	Refuse to file letter #1
07/06/95	Refuse to file letter #2
08/09/95	Acknowledgement letter
01/18/96	Bio deficiency letter
01/29/96	NA letter (from CR #1 by S.Liu & LR #1 by C.Holquist)
02/05/96	Telecon (Re: revision of bio letter of 01/18/96)
07/24/96	NA (MINOR)(from CR #2 dated 07/16/96 by S.Liu)
08/22/96	Bio acceptance letter
09/24/96	NA letter (from CR #3 by S.Liu)

10. **PHARMACOLOGICAL CATEGORY:** See CR #1.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** See CR #1.

13. **DOSAGE FORM:** Tablets

14. **POTENCY:**
Single Strength: Orphenadrine Citrate/Aspirin/Caffeine
(25 mg/385 mg/30 mg)

Double Strength: Orphenadrine Citrate/Aspirin/Caffeine
(50 mg/770 mg/60 mg)

15. **CHEMICAL NAME AND STRUCTURE**: See CR #1.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
EER is acceptable as of 03/29/96. Bio is acceptable on 08/22/96. Method validation request was issued on 08/01/96. A memo dated 12/02/96 from the Northeast Regional Laboratory indicated that Eon's method appears to be suitable for regulatory analysis of the drug product.

In the last NA letter, DMF deficiency was the only deficiency. Eon responded the NA letter after they had been informed by the holder of chat response to the DMF deficiencies were submitted to FDA. Now all three drugs substances DMF are adequate.

Labeling is now satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approvable. An approval summary will be prepared.

19. **REVIEWER**: Shing H. Liu, Ph.D. **DATE COMPLETED:** Completed 12/10/96

cc: ANDA 74-654
DUP JACKET
Division File
FIELD COPY

Endorsements:
HFD-625/S.Liu/12/10/96 Shing Hon Liu 12/19/96
HFD-625/M.Smela/12/11/96
x:\new\firmsam\eon\ltrs&rev\74654CR4.APP
F/T by: gp/12/16/96

M Smela 12/19/96

D.J

ANDA 74-654

JAN 18 1996

Eon Laboratories, Inc.
Attention: Edward Shinal
227-15 Conduit Ave.,
Laurelton, NY 11413

Dear Dr. Shinal:

Reference is made to the Abbreviated New Drug Application, submitted on March 24, 1995, for Orphenadrine Citrate, Aspirin, and Caffeine Tablets.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. We advise the submission of all pre-dose chromatograms (i.e., subjects #1-4, 6-36) for orphenadrine. Included should be details on the chromatogram acceptance criteria, especially with regard to peak overlap and interferences.

2. The final report excluded the first fourteen subjects from orphenadrine statistical analysis after using a previously validated analytical method, because of an interference peak. After revalidation of the method, subjects #16, 24 and 25 also were excluded from orphenadrine statistical analysis because of an insufficient number of samples with values, due to analytical problems. Explain these problems and the reasons for these problems after the revalidation of the methods. Exclusion of these three subjects, after revalidation of the method due to analytical problems, raises questions regarding the analytical method.

3. Submit stability data for orphenadrine in frozen plasma up to 167 days.

4. Conduct the dissolution testing on its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg Tablets at 15, 30, 45 and 60 minutes sampling times. The dissolution testing should be conducted in 900 mL of water @ 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of Aspirin and Caffeine in the dosage form is dissolved in 45 minutes.
   Not less than of the labeled amount of Orphenadrine Citrate in dosage form is dissolved in 60 minutes.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

DEC 2 1 1995 D.J

Orphenadrine Citrate/Aspirin/Caffeine
50 mg/770 mg/60 mg Tablet
ANDA #74-654
Reviewer: Moheb H. Makary
WP 74654SDW.395

Eon Labs Manufacturing Inc.
Laurelton, N.Y.
Submission Date:
March 24, 1995

Review of a Bioequivalence Study and Dissolution Data

Objective:

The objective of this study was to compare the plasma levels of orphenadrine, aspirin (acetylsalicylic acid and salicylic acid) and caffeine, after administration of single dose of 50 mg/770 mg/60 mg of the test formulation (Eon's Orphenadrine Citrate, Aspirin, and Caffeine Tablet, 50 mg/770 mg/60 mg) with that of 3M reference product (Norgesic^{R} Forte Tablet, 50 mg/770 mg/60 mg) under fasting conditions. The firm requested a waiver of the *in vivo* bioequivalence testing requirements for its 25 mg/385 mg/30 mg strength. Dissolution profiles comparing Eon's Orphenadrine Citrate, Aspirin and Caffeine , 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg tablets and Norgesic® 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg tablets were submitted. Comparative compositions were also submitted.

Introduction:

Orphenadrine is an analogue of the antihistamine, diphenhydramine. It is a centrally acting (brain stem) compound indicated, in combination with aspirin and caffeine, for the symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.

Both orphenadrine and the salicylate (the active metabolites of aspirin) reach peak plasma levels several hours after oral dosing. The elimination half-life of orphenadrine is about 14-16 hours, that of aspirin is 0.25 hour, the salicylate 3-12 hours and caffeine about 5 hours.

The combination product is commercially available as Norgesic^{R}, manufactured by 3M pharmaceuticals.

Single Dose Bioequivalence Study #9316701B Under Fasting conditions:

Clinical site:

Analytical site:

Investigators: Clinical Investigator

Study design: Open-label, randomized, 2-way crossover, single-dose study under fasting conditions.

Subjects: Thirty-six (36) male subjects between 18 to 55 years of age were accepted for entry into the clinical portion of the study and 35 completed the entire study during the time period 7/30/93 to 8/16/93. Subjects were within ±15% of their ideal weight as specified in the protocol with the exception of four subjects. The height of two subjects exceeded the maximum and the height of one subject was below the minimum on the Metropolitan Life Insurance Bulletin chart (1983). The subjects' height and weight were considered proportional and were approved for entry into the study. One subject was slightly over the maximum ideal weight but was permitted to enter the study by the investigator. The subjects were selected on the basis of acceptable medical histories and normal physical examinations that showed no clinically significant chronic disease.

Exclusion criteria:

* History of adverse reactions or allergy to orphenadrine, aspirin, caffeine or other nonsteroidal, anti-inflammatory drugs or to any salicylate drugs.
* Presence of any clinical relevant abnormality identified in the screening of physical or laboratory examinations.
* Any subject who has received an investigational drug within four weeks prior to entry into the study.

Restrictions: Subjects were instructed not to take any medications, including aspirin and OTC preparations from two weeks prior to the first drug administration until after the study. Alcohol, xanthine-or caffeine containing beverages and food prohibited from 48 hours prior to dosing and until after completion of the study.

Dose and treatment: All subjects completed an overnight fast. No

meals were served within 4 hours of any of the following treatments:

A. Test product: 1 x 50 mg/770 mg/60 mg Orphenadrine Citrate, Aspirin and Caffeine Tablet (Eon), lot #930502, lot size tablets, content uniformity 101.9%, 98.4% and 101.9%, potency 97.4%, 98.9% and 100.4% for Orphenadrine, Aspirin and Caffeine, respectively.

B. Reference product: 1 x 50 mg/770 mg/60 mg Norgesic® Tablet (3M pharmaceuticals), lot #930572, Exp. 5/96.

Washout period: two weeks

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. Dinner was served ten hours after dosing. Water (240 mL) was given with the dose. Water intake was permitted ad lib after 2 hours post-dose.

Blood samples: Blood samples were collected at 0 (pre-dose), 0.17, 0.33, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours. Two subjects each missed two return blood collections but were allowed to continue in the study by the investigator. Blood samples were collected in grey-top tubes (potassium oxalate/sodium fluoride additive) at each sampling time (20 mL at 0-24 hours and 15 mL at 36-72 hours). The plasma was transferred to three storage tubes containing physostigmine sulfate preservative. The plasma samples intended for orphenadrine and caffeine analyses were stored frozen at -20°C until transfered to the laboratory. The plasma samples intended for aspirin analysis (0-24 hours samples only) were flash frozen and stored at -70°C until analysis. The plasma concentrations of orphenadrine, acetylsalicylic acid, salicylic acid and caffeine were measured up to 72, 6, 24 and 24 hours, respectively.

Safety Evaluations: Blood pressure, pulse rate, respiratory rate and oral temperature were measured during each check-in and approximately one hour before each dosing.

Analytical Methodology

Statistical Analysis

Statistical analysis was performed on orphenadrine, acetylsalicylic acid, salicylic acid and caffeine data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The data analyzed by ANOVA were also performed for blood drug concentrations at each sampling time. The 90% confidence intervals using the two one-sided t test method were calculated for AUC(0-t), AUCinf and Cmax for each analyte.

In Vivo Results:

Thirty-six (36) healthy male subjects were entered into the clinical phase of the study. Thirty-five (35) subjects successfully completed both phases of the study. Subject #5 was dropped study after the 1.5 hour blood collection in period I due to poor venous access. Six subjects experienced headache, lightheadedness, dizziness, diaphoretic, drowsiness and nervousness. None of the adverse events experienced by the subjects during the study were judged as serious.

Plasma concentrations of orphenadrine up to 72 hours were determined for the first 14 subjects using a previously validated method but an interfering peak was apparent that could not be resolved. The assay was stopped and the analytical procedure was modified and validated. Plasma concentrations of orphenadrine were determined on subjects 15 through 36 using the newly modified

method. The chronology of events for orphenadrine analysis are shown in Table 1.1. In addition, subjects' data excluded from orphenadrine statistical analysis and the reasons for exclusion are shown in Table 2.1.

The plasma levels and pharmacokinetic parameters for orphenadrine in nineteen (N=19) and fourteen (N=14) subjects are summarized below:

Table III

Mean Plasma Orphenadrine Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 50 mg/770 mg/60 mg Orphenadrine Citrate, Aspirin and Caffeine (1 Tablet) Under Fasting Conditions
(N=19)

Time hr	Eon Test Product Lot# 930502 ng/mL (CV)	3M Reference Product Lot# 930572 ng/mL (CV)
0	0.00	0.00
0.17	0.00(0.00)	0.18 (412.3)
0.33	0.00(0.00)	0.00 (.)
0.5	0.35(424.3)	0.35 (424.3)
1	8.23(76.7)	7.51 (107.4)
1.5	26.72(48.2)	23.41 (54.0)
2	36.51(33.1)	34.42 (37.9)
3	47.24(30.7)	44.72 (29.6)
4	46.74(27.6)	44.13 (26.5)
5	42.33(30.9)	41.59 (26.8)
6	38.10(30.8)	36.96 (26.9)
8	31.72(27.7)	31.48 (29.2)
12	22.35(31.8)	22.48 (29.8)
16	17.82(33.8)	17.10 (32.8)
24	13.66(36.3)	13.69 (34.5)
36	8.37(33.8)	8.54 (37.3)
48	5.38(52.0)	5.35 (51.9)
60	2.71(94.9)	2.59 (91.9)
72	1.33(154.4)	1.31 (153.0)
	Mean (CV)	Mean (CV) 90% CI
AUC(0-t) ng.hr/mL	853.88(35.9)	850.53(33.1)
AUCinf ng.hr/mL	976.28(33.9)	969.22(31.1)
CMAX (ng/mL)	48.95(29.5)	47.29(27.1)
Kel (1/hr)	0.0357	0.0346

Half (hr)	20.53	21.10	
TMAX(hr)	3.54	3.43	
LnAUC(0-t)			94.2-105.6%
LnAUCi			98.5-104.7%
LnCmax			98.8-107.4%

Table IV

Mean Plasma Orphenadrine Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 50 mg/770 mg/60 mg Orphenadrine Citrate, Aspirin and Caffeine (1 Tablet) Under Fasting Conditions
(N=14)

Time hr	Eon Test Product Lot# 930502 ng/mL (CV)	3M Reference Product Lot# 930572 ng/mL (CV)
0	0.00(.)	0.00 (.)
0.17	0.00(.)	0.00 (.)
0.33	0.00(0.00)	0.00 (.)
0.5	0.38(374.2)	0.49 (360.6)
1	7.77(85.3)	7.89 (111.3)
1.5	27.06(55.5)	22.56 (56.6)
2	36.44(36.1)	35.35 (40.6)
3	44.54(31.1)	44.36 (31.9)
4	44.89(29.3)	44.11 (28.0)
5	39.38(28.0)	40.29 (28.3)
6	36.58(29.5)	35.86 (28.6)
8	30.54(26.1)	30.76 (29.9)
12	21.34(32.6)	22.55 (31.0)
16	16.88(33.9)	16.83 (35.1)
24	12.66(31.1)	13.16 (37.0)
36	8.09(34.1)	8.50 (39.7)
48	4.94(56.6)	4.83 (51.2)
60	2.24(108.5)	2.45 (95.6)
72	1.11(167.3)	0.95 (200.9)
	Mean (CV)	Mean (CV) 90% CI
AUC(0-t) ng.hr/mL	805.72(35.9)	817.26(34.2)
AUCinf ng.hr/mL	919.21(32.7)	929.37(32.8)

CMAX (ng/mL)	46.57(29.6)	46.75(29.6)
Kel (1/hr)	0.0375	0.0355
Half (hr)	19.33	20.82
TMAX(hr)	3.58	3.44

LnAUC(0-t)	90.6-105.2%
LnAUCi	96.7-103.7%
LnCmax	95.3-103.6%

Plasma Orphenadrine:

1. The orphenadrine plasma levels (N=19) peaked at 3 hours for both the test and the reference products. The levels within each drug were similar. There were no statistically significant differences between the plasma orphenadrine levels at all sampling time points.

2. The data demonstrate that there are no statistically significant differences for orphenadrine between the test and the reference product for AUC(0-t), AUCi and Cmax. Differences from the least squares reference means of -0.3%, -2.3% and -3.5% for orphenadrine AUC(0-t), AUCi and Cmax, respectively, were observed. The 90% confidence intervals for each of the above parameter are within the acceptable range of 80-125%. The reviewer's calculations are same as those submitted by the firm.

3. The firm excluded subjects with missing values which either could have been the peak drug concentration (subjects #15, 20, 33 and 36), or could cause inaccurate AUC (subject #30). After excluding these subjects from the statistical analysis of the study (N=14) for the reasons mentioned above, the resulting 90% confidence intervals for orphenadrine are as following:

LnAUC(0-t)	90.6-105.2%
LnAUCi	96.7-103.7%
LnCmax	95.3-103.6%

All confidence intervals remain within the acceptable 80-125% range.

Formulations:

Eon's formulations for its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg Tablets are shown below:

Component	**25/385/30 mg MG Per Tablet**	**50/770/60 mg MG Per Tablet**
Orphenadrine Citrate, USP	25.0	50.0
Aspirin		
*Aspirin, USP		

Caffeine, USP		
Anhydrous Lactose, NF		
Microcrystalline Cellulose, NF		
Pregelatinized Starch, NF		
Croscarmellose Sodium, NF		
Povidone, USP		
Stearic Acid, NF		
Sodium Lauryl Sulfate, NF		
Colloidal Silicon Dioxide, NF		
Purified Water, USP		
Total	**640.00 Mg**	**1280.0 mg**

The amounts listed above for Orphenadrine Citrate, Aspirin, and Caffeine are based on potency of 100.0%.
+ Contains FD&C Yellow No. 10 and FD&C Blue No. 1 color additives.

In Vitro Dissolution Testing

Method:	USP 23 apparatus 2 at 50 rpm
Medium:	900 mL of water
Sampling Time:	15, 30, 45 and 60 minutes, for the 25/385/30 mg strength and 15, 30 and 60 minutes for the 50/770/60 mg strength.
Number of Tablets:	12
Test Products:	Eon's Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/770 mg/60 mg, lot #930502 25 mg/385 mg/30 mg , lot # 940110
Reference Products:	3M's Norgesic Tablets 50 mg/770 mg/60 mg, lot #930572 25 mg/385 mg/30 mg, lot #930214

The dissolution testing results are presented in Table V.

Deficiency Comments:

1. The firm is advised to submit all pre-dose chromatograms (i.e., subjects #1-4, 6-36) for orphenadrine. The firm should submit details on its chromatogram acceptance criteria with regard to peak overlap and interferences.

2. The firm excluded the first fourteen subjects from orphenadrine statistical analysis after using a previously validated analytical method, because of an interference peak. After the firm revalidated the method, subjects #16, 24 and 25 were excluded from orphenadrine statistical analysis because of an insufficient number of samples with values due to analytical problems. The firm should explain these analytical problems and the reasons for these problems after the firm had revalidated the method. Excluding these three subjects after revalidation of the method due to analytical problems raises

questions regarding the analytical method.

3. The firm should submit stability data for orphenadrine in frozen plasma up to 167 days.

4. The firm should conduct the dissolution testing on its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg Tablets at 15, 30, 45 and 60 minutes sampling times. The dissolution testing should be conducted in 900 mL of water @ 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of Aspirin /Caffeine in the dosage form is dissolved in 45 minutes.
> Not less than of the labeled amount of Orphenadrine Citrate in dosage form is dissolved in 60 minutes.

Comments:

1. The firm has submitted the plasma concentrations and pharmacokinetic parameters for aspirin (acetylsalicylic acid and salicylic acid) and caffeine. Since Aspirin and Caffeine do not require bioequivalence testing based on the Agency memo dated May 4, 1995, and the fact that both products are AA rated, these data have not been reviewed.

2. For Orphenadrine, statistical analyses were performed on the major pharmacokinetic parameters using 19 and 14 subjects. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% in both analyses.

3. The 25 mg/385 mg/30 mg tablet is compositionally proportional to the 50 mg/770 mg/60 mg tablet.

4. The firm's in vitro dissolution testing for its Orphenadrine Citrate, Aspirin and Caffeine Tablets, 25 mg/385 mg/30 mg is acceptable. The in vitro dissolution testing for its Orphenadrine Citrate, Aspirin and Caffeine Tablets, 50 mg/770 mg/60 mg is incomplete.

5. Orphenadrine Citrate, Aspirin and Caffeine Tablets, 25 mg/385 mg/30 mg, and 50 mg/770 mg/60 mg, manufactured by Eon Labs Manufacturing Inc., exhibited higher mean values of dissolution for Caffeine and Orphenadrine than the reference products.

Recommendations:

1. The single-dose bioequivalence study #9316701B under fasting conditions conducted by Eon Labs Manufacturing Inc., on its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg

Tablet, lot #930502, comparing it to Norgesic[R] Forte 50 mg/770 mg/60 mg Tablet, manufactured by 3M Pharmaceuticals, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments 1-3.

2. The dissolution testing conducted by Eon Labs Manufacturing Inc., on its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg, lot #930502, is incomplete for the reason cited in deficiency comment #4.

3. Waiver of in vivo bioequivalence study requirements for Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg Tablet is pending until the study of the 50 mg/770 mg/60 mg strength is acceptable.

The firm should be informed of the deficiency comments and recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramanand M Mhatre Date: 12/21/95

Concur: See CC 12 9. Memo Date:
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/12-20-95 wp 74654SDW.395
cc: ANDA#74-654 original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table V. In Vitro Dissolution Testing

Drug (Generic Name): Orphenadrine Citrate, Aspirin and Caffeine
Dose Strength: 50/770/60 mg and 25/385/30 mg
ANDA No.: 74-654
Firm: Eon
Submission Date: March 24, 1995
File Name: 74654SDW.395

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Water
Specifications: NLT in 45 minutes (Aspirin/Caffeine) in 60 miutes (Orphenadrine).
Reference Drug: Norgesic
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Aspirin

Sampling Times (Minutes)	Test Product Lot # 940110 Strength(mg) 25/385/30 mg			Reference Product Lot # 930214 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	73.5		9.6	71.6		6.8
30	85.8		6.1	83.1		4.9
45	85.2		4.4	87.4		4.3
60	84.9		3.9	87.7		3.9

Caffeine

Sampling Times (Minutes)	Test Product Lot # 940110 Strength(mg) 25/385/30			Reference Product Lot # 930214 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	95.9		8.0	56.8		27.7
30	100.3		4.3	76.3		17.8
45	100.0		3.5	87.1		10.5
60	99.5		3.5	90.0		6.3

II. Results of In Vitro Dissolution Testing: Orphenadrine Citrate

Sampling Times (Minutes)	Test Product Lot # 940110 Strength(mg) 25/385/30			Reference Product Lot # 930214 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.5		8.2	60.7		27.5
30	100.8		3.6	82.3		17.7
45	102.5		3.9	95.9		9.8
60	104.1		3.3	102.3		4.9

II. Results of In Vitro Dissolution Testing: Aspirin

Sampling Times (Minutes)	Test Product Lot # 930502 Strength(mg) 50/770/60			Reference Product Lot # 930572 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	63.9		10.9	62.6		11.2
30	83.5		8.7	82.0		10.2
60	95.4		5.3	93.2		4.4

II. Results of In Vitro Dissolution Testing: Caffeine

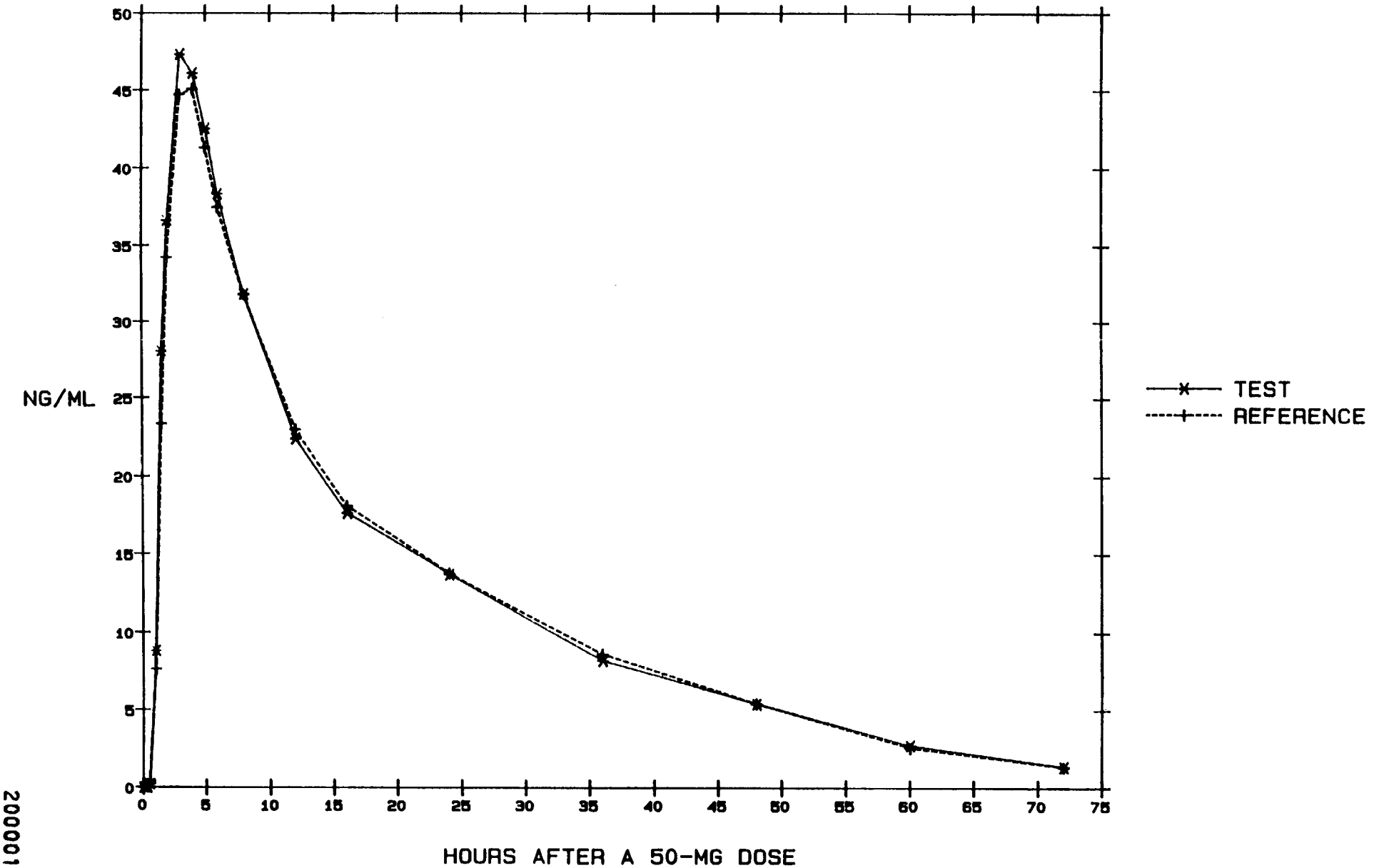
Sampling Times (Minutes)	Test Product Lot # 930502 Strength(mg) 50/770/60			Reference Product Lot # 930572 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	84.6		16.3	59.4		32.1
30	94.0		7.9	88.1		15.5
60	98.3		3.6	102.2		4.3

II. Results of In Vitro Dissolution Testing: Orphenadrine Citrate

Sampling Times (Minutes)	Test Product Lot # 930502 Strength(mg) 50/770/60			Reference Product Lot # 930572 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86.1		15.2	60.2		23.6
30	95.9		7.1	87.8		15.3
60	100.8		4.3	100.7		4.8

STUDY NO. 93167018

LEAST SQUARES MEAN ORPHENADRINE PLASMA CONCENTRATIONS IN 19 MEN



200001

ANDA 74-654

Eon Labs. Manufacturing, Inc.
Attention: Yau-Kit Lam
227-15 North Conduit Avenue
Laurelton NY 11413

AUG 22 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Orphenadrine Citrate Aspirin Caffeine Tablets 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   NLT in 45 minutes for Aspirin and Caffeine
   NLT in 60 minutes for Orphenadrine Citrate

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 16 1996

Orphenadrine Citrate/Aspirin/Caffeine
50 mg/770 mg/60 mg Tablets
25 mg/385 mg/30 mg Tablets
ANDA #74-654
Reviewer: Moheb H. Makary
WP 74654SDW.496

Eno Lab Manufacturing Inc
Laurelton, N.Y.

Submission Date:
April 22, 1996

Review of An Amendment to Bioequivalence Study

I. Objective:

The firm has replied to the reviewer's comments made in the review of the March 24, 1995 submission (a bioequivalence study on Orphenadrine Citrate/Aspirin/Caffeine Tablets, 50 mg/770 mg/60 mg, dissolution data and waiver request).

II. Comment #1

The firm was asked to submit all pre-dose chromatograms (i.e., subjects #1-4, 6-36) for orphenadrine and details on the chromatograms acceptance criteria.

The firm submitted all pre-dose chromatograms for all subjects in the study and copies of three versions of SOP #3400 (Acceptance and Recording Chromatographic Data).

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm excluded the first fourteen subjects from the statistical analysis of the study because of an interference peak. After revalidation of the analytical method, the firm excluded another three subjects (#16, 24 and 25) from the statistical analysis of the study, due to analytical problems. The firm was asked to explain these exclusions after revalidation of the analytical method.

The firm indicated that the primary cause of excluding the subjects was unavailability of adequate sample volume to quantitate all four analytes (Orphenadrine, Acetylsalicylic acid, Salicylic acid and Caffeine). Following the modification and revalidation of the analytical method, data for subject #16 were unreportable due to Data for subjects #24 and 25, which processed and analyzed together against the same standard curve, were unreportable due to

It should be noted that the firm in the current review indicated that subject #9 which excluded from the study analysis because of an interference peak (among subjects #1-14) should have been included in the study. The reported interference was, in fact, within the limits of acceptability. After including subject #9 in the statistical analysis of the study (N=20 or N=15), the 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax remained within the acceptable range of 80-125%.

Reply to Comment #2

The firm's response to the comment is acceptable.

Comment #3

The firm was asked to submit stability data for orphenadrine in frozen plasma up to 167 days.

The firm submitted data to support the stability of orphenadrine in heparinized (-15 ± 5°C) plasma up to 1208 days.

Reply to Comment #3

The firm's response to the comment is acceptable.

III. Comments:

1. The firm has submitted the plasma concentrations and pharmacokinetic parameters for aspirin (salicylic acid) and caffeine. Since Aspirin and Caffeine do not require bioequivalence testing based on the Agency memo dated May 4, 1995, and the fact that both products are AA rated, these data have not been reviewed.

2. An inspection request for routine audit for the orphenadrine citrate portion of the study was issued to the Division of Scientific Investigations. The clinical case report for subject #35 was not available in the designated study box and could not be located during the inspection. The audit report recommended that the data from subject #35 should be excluded from the final data analysis. After excluding subject #35 from the statistical analysis of the study, the 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax remained within the acceptable range of 80-125%.

3. For Orphenadrine, the firm's in vivo bioequivalence study under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions.

4. The 25 mg/385 mg/30 mg tablet is proportionally similar to the 50 mg/770 mg/60 mg tablet.

5. The firm's in vitro dissolution testing for its Orphenadrine Citrate, Aspirin and Caffeine, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg tablets is acceptable.

IV. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Eno Lab Manufacturing Inc., on its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg Tablet, lot #930502, comparing it to Norgesic® Forte 50 mg/770 mg/60 mg Tablet, manufactured by 3M Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eno's Orphenadrine Citrate, Aspirin and Caffeine Tablet, 50 mg/770 mg/60 mg is bioequivalent to the reference product, Norgesic® Forte Tablet, 50 mg/770 mg/ 60 mg, manufactured by 3M Pharmaceuticals.

2. The dissolution testing conducted by the firm on its Orphenadrine Citrate, Aspirin and Caffeine Tablets, 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg, lot #930502 and #940110, respectively, is acceptable. The formulation for the 25 mg/385 mg/30 mg strength is proportionally similar to the 50 mg/770 mg/30 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 25 mg/385 mg/30 mg tablet of the test product is granted. The Division of Bioequivalence deems Orphenadrine Citrate, Aspirin and Caffeine tablets, 25 mg/385 mg/30 mg, manufactured by Eno Lab Manufacturing Inc., to be bioequivalent to Norgesic® Tablets, 25 mg/385 mg/30 mg, manufactured by 3M Pharmaceuticals.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT	in	minutes for Aspirin and Caffeine
NLT	in	minutes for Orphenadrine Citrate

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III